Remarks

I. Introduction

By this amendment, Applicant cancels claims 17-30, 46-58 and 69 without prejudice to pursue these claims in a continuation application. Claims 59-67 and 69-71 are pending. Claims 59 and 70 are amended. No new matter is introduced in these claims. This response and amendment are timely filed in view of the accompanying petition for a two month extension of time and the required fee. Applicant respectfully requests that the Examiner consider the following remarks and allow the pending claims.

II. Interview with Examiner

Applicant would like to thank Examiner Jennifer Kim and her supervisor, Examiner Sreenivasan Padmanabhan, for their time and consideration during the interview with Applicant's representatives on June 27, 2007. Applicant agrees with the substance of the Examiner's Interview Summary.

III. Rejections

A. Claims 17-26, 29, 46-55 and 58-71 are provisionally rejected on the basis of nonstatutory obviousness-type double patenting over co-pending application serial number 11/111,435. Claims 17-30, 46-58 and 69 have been canceled, rendering moot their rejection. Applicant respectfully requests deferral of the rejection until such time that allowable subject matter is found in both applications.

B. Claims 17-26 and 29 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gerra et al. (*Current Therapeutic Research*, 1991, hereinafter Gerra) in view of Nutt et al.

(*Alcohol and Alcoholism*, 1993, hereinafter Nutt), of record. These claims have been canceled, rendering their rejection moot.

C. Claims 27 and 28 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Gerra and Nutt, as applied to claims 17-26 and 29 further in view of U.S. Patent No. 5,519,017 to Opitz (hereinafter Opitz). These claims have been canceled, rendering their rejection moot.

D. Claims 30, 46-55, 58-68 and 71 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Gerra and Nutt, as applied to claims 17-26 and 29 further in view of Soderpalm et al. (Psychopharmacology, 1998, hereinafter Soderpalm). Claims 30 and 46-55 and 58 have been canceled, rendering their rejection moot. Accordingly, claims 59-68 and 71 stand rejected. Applicant respectfully traverses this rejection for the following reasons and asserts that the claims, as amended, are allowable.

As the Examiner has stated on the record, neither Gerra nor Nutt discloses reduction of the desire to drink alcohol by flumazenil. Soderpalm is also silent concerning reduction of a desire to drink alcohol.

1) *Soderpalm*

Soderpalm uses flumazenil for a different endpoint than Applicant's claimed invention. Soderpalm uses flumazenil to decrease benzodiazepine (midazolam)-induced increased taste reactivity to ethanol following ethanol infusion into the oral cavity of rats. The increased taste reactivity to ethanol was caused by the previous administration of the benzodiazepine, midazolam.

Flumazenil is a benzodiazepine antagonist. Flumazenil given alone "exerted no significant effect on alcohol taste reactivity" in comparison to vehicle treated controls (Page 219, left column, first paragraph, page 220, first col., last paragraph, figure 4). Accordingly, Soderpalm does not disclose or suggest that flumazenil decreases taste reactivity to alcohol in rats. In fact, Soderpalm states that flumazenil by itself had no significant effect. Flumazenil was only effective to blunt the effect of midazolam to stimulate taste reactivity to alcohol in rats.

Soderpalm evaluated the hedonic response to alcohol as "Taste reactivity testing and scoring" (page 216, second column, second and third paragraphs). The test animals had a catheter implanted such that the opening was near the first upper molar. In the test condition, alcohol was infused into the oral cavity (1 ml of 6% ethanol in 1 minute). Then mouth movements and tongue protrusions were combined to form a hedonic taste reactivity score.

Applicant respectfully asserts that hedonic orofacial responses in rats (palatability to infused ethanol) are not equivalent to reducing a desire to drink alcohol in humans. Soderpalm did not test the effect of flumazenil on any behaviors related to a desire to drink alcohol in humans. The alcohol was infused into the oral cavity of the test animals. Alcohol taste reactivity in animals with ethanol infused into the oral cavity is different from a desire to drink in humans.

In contrast to Soderpalm, Applicant administers flumazenil to decrease the desire to drink alcohol. Therefore, Soderpalm teaches a different method to achieve a different result, namely, use of flumazenil to reduce benzodiazepine-stimulated taste reactivity to ethanol in

rats. In contrast, Applicant administers flumazenil in a specific dose regimen, to patients who have a desire to drink alcohol in order to reduce their desire to drink alcohol.

One of skill in the art of reducing the desire to drink alcohol would not combine Soderpalm with Gerra and Nutt as: 1) One of skill in the art of reducing the desire to drink alcohol in humans would not look to art concerning midazolam-induced taste reactivity to alcohol in rats; 2) taste reactivity to ethanol infused into the oral cavity of rats is different from reducing the desire to drink alcohol in humans; and, 3) Soderpalm observed that administration of flumazenil without a benzodiazepine had no effect on taste reactivity to alcohol. Therefore, Soderpalm is improperly combined with Gerra and Nutt, who address withdrawal symptoms, in the §103 rejection and should be withdrawn.

2) *Gerra, Nutt and Soderpalm*

As stated above, and as stated by the Examiner, Gerra and Nutt are silent as to the use of flumazenil to reduce the desire to drink alcohol in a patient. This alone is sufficient to establish that Gerra and Nutt are improperly combined with Soderpalm in a §103 rejection of Applicant's pending claims, as Soderpalm is also silent as to a reduction in desire to drink alcohol and further demonstrates that flumazenil alone had no effect. The combination of references does not in any way disclose, suggest or provide motivation to one of ordinary skill in the art to administer flumazenil in the claimed dosing regimen to reduce the desire to drink alcohol in patients. In addition, Applicant's claimed dosing regimen recited in Claim 59 is not disclosed in the cited art.

While Examiner's official communications have not expressly grounded any claim rejections based upon an assertion that the claimed invention was inherently practiced in the

prior art, during the course of the interviews, Examiner Kim and Supervisor Padmanabhan adopted the position that the experiments conducted in Gerra and Nutt *may* have inherently practiced the claimed invention. Specifically, although the studies in Gerra and Nutt were not designed to study the desire to drink alcohol, did not mention the concept of reducing the desire to drink alcohol, and did not use the claimed administration protocol, a belief was expressed that Gerra and/or Nutt may inherently disclose the claimed invention.

This belief, if it in fact forms an unstated basis for the pending rejections, is legally and factually erroneous for two reasons: a) there is no evidentiary or legal basis for assuming that treating alcohol withdrawal symptoms, or midazolam-induced increases in taste reactivity, necessarily reduces a patient's desire to drink alcohol; and, b) the prior art clearly teaches that the administrative protocol matters—Gerra, Nutt and Soderpalm achieved different therapeutic results using different flumazenil administrative protocols—thereby, making it scientifically untenable to assume that two different administrative protocols would necessarily result in the same therapeutic result.

a) Treating alcohol withdrawal symptoms, or midazolam-induced increases in taste reactivity, does not necessarily reduce a patient's desire to drink alcohol.

Inherency is only found when the invention "necessarily follows" or is a "natural result following from" practicing a process described in a prior art reference. A case with analogous facts is Rapoport v. Dement, 254 F.3d 1053 (Fed.Cir. 2001). In Rapoport, the court addressed the patentability of a claim for "a method for the treatment of sleep apnea", which was formulated in the course of an interference proceeding. The relevant part of the claim at issue provides:

> 1. A method for treatment of sleep apneas comprising administration of a therapeutically effective regimen of a Formula I azapirone compound or a pharmaceutically effective acid addition salt thereof to a patient in need of such treatment....

The Board of Appeals declared Dement to be the senior party and, in response, Rapoport filed a motion claiming that a prior art publication, authored by Rapoport, rendered the claims anticipated and/or obvious. At issue, then, was whether Rapoport's publication (the "FPR Publication") disclosed the claimed method.

Among other arguments, Rapoport asserted that the FPR Publication disclosed a method of treating a secondary symptom related to sleep apnea, anxiety, using buspirone, which all parties agreed is within the definition of a "Formula I azapirone compound". Therefore, according to Rapoport, the FPR Publication discloses the administration of a therapeutically effective regimen of Formula I azapirone compound (buspirone) in a manner that would inherently treat sleep apnea and, thus, the claim is anticipated.

The Federal Circuit clearly rejected this argument and deemed it "without merit". See Id. at 1062. For the FPR Publication's disclosure to be anticipating, one must assume that a person would have used the buspirone in the precise manner required to actually treat sleep apnea (as opposed to anxiety), even though that specific administration protocol, and the objective of treating sleep apnea, was never disclosed in the FPR Publication. Treating anxiety, even though related to sleep apnea, is simply not the same as treating sleep apnea and, therefore, a publication that discloses the use of a drug to treat anxiety cannot anticipate the use of that same drug to treat sleep apnea. The Federal Circuit concluded

"[i]nherency...may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." Id. at 1063 (citing Cont'l Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed.Cir.1991)). See also *Glaxo Group v. Teva Pham. USA, Inc.*, No. CIV.A.02-219 GMS, 2004 WL 1875017, at *18-20 ("Although inherent anticipation does not require the element to be present each and every time, it does require the result to be a necessary and inevitable consequence of practicing the invention claimed in the prior art under normal conditions." Glaxo, 2004 WL 1875017, at *19. (emphasis added)).

In the present case, treating alcohol withdrawal symptoms with flumazenil or reducing midazolam-induced increases in taste reactivity to rats do not inherently anticipate reducing the desire to drink alcohol. Following the cessation of withdrawal symptoms, the cravings or desire to drink in alcohol dependent individuals typically persist. Also, as stated above, midazolam-induced taste reactivity in rats is not related to a reduction in the desire to drink alcohol. Accordingly, a reduction in the cravings or desire to drink alcohol is not a necessary and inevitable consequence of the use of flumazenil to treat withdrawal symptoms. As in Rapoport, it is without merit to assert that treating alcohol withdrawal symptoms, particularly using a claimed administration protocol not disclosed in the prior art, can anticipate a treatment that reduces a patient's desire to drink alcohol.

Treatment of alcohol withdrawal symptoms is recognized by those of ordinary skill in the art as different from treatment of alcohol dependence. Exhibit A (filed in the last response) is an article by Bayard et al., (American Family Physician 2004 :69:1443-1450)

which clearly indicates on page 1443 (Abstract) and on 1448, second column, fourth paragraph, that

> "Treatment of alcohol withdrawal syndrome should be followed by treatment for alcohol dependence. Treatment of withdrawal alone does not address the underlying disease of addiction and therefore offers little hope for long-term abstinence."

Addicts have a desire to drink alcohol. Bayard et al., clearly indicate that treatment of alcohol withdrawal symptoms is recognized as different from treatment of alcohol dependence. There is no support in the Office Action for the assumption that these treatment methods are equivalent. In fact, the art (Bayard et al.) indicates these treatments are different and not equivalent. For at least these reasons, Applicant asserts that the rejection in view of Gerra, Nutt and Soderpalm under 35 U.S.C. §103(a) has been overcome and requests its withdrawal.

b) The cited references do not teach or suggest the claimed dosing regimen

The dosage regimens described by the prior art are either a two-day process (Gerra), a one-minute bolus dose (Nutt), or a single ip injection (Soderpalm). None of the references, alone or in combination, teaches, suggests or provides motivation to use the claimed amount (0.1-0.3 mg) of flumazenil administered sequentially over 1 to 15 minutes for any purpose. As discussed above, none of the references, alone or in combination, teaches, suggests or provides motivation to use flumazenil in the claimed administrative schedule to reduce the cravings and desire to drink alcohol.

- Gerra - doses of 0.5 mg every six hours for 48 hours (for a total of 2 mg/day) to treat withdrawal. 0.5 mg in 360 minutes is about 0.00138 mg/min or 1.38 ug/min. This is about 72 times less than Applicant's recited 0.1 mg/min and about 217 times less than Applicant's recited 0.3 mg/min.
- Nutt – a dose of 2 mg over 1 minute (for a total of 2 mg/day). Nutt's administration caused sweating and anxiety. Applicant's regimen is 0.1 to 0.3 mg between 1 and 15 minutes which is about 6.7 to 20 times less than Nutt's paradigm, and 100 to 333 times less than Nutt's paradigm when spread over the recited 15 minute period.
- Soderpalm – a dose of 10 mg/kg ip given in 10 ml of water plus Tween 80 to rats. If Soderpalm's rats were about 300 gm in body weight, then the rats received about 3 mg of flumazenil. Administration of 10 mg/kg to a 70 kg patient would equate to a total dose of 700 mg, which is 350 times greater than Applicant's dose of about 2 mg/day.

The differences in flumazenil dosing protocols are clearly significant as Gerra's and Nutt's protocols produced different results, and as Soderpalm demonstrated that flumazenil alone had no effect on a different endpoint (taste reactivity).

The regimens of the prior art were designed in order to measure the effects of flumazenil on withdrawal – i.e., the acute symptoms of elevated temperature, increased blood pressure, rapid heart rate, restlessness, psychosis, and seizures. In fact, the effects of flumazenil reported by Nutt were quite variable, in most patients causing increased sweating and anxiety (page 337, Abstract; page 339, 2nd full paragraph). In some of Nutt's patients withdrawal symptoms disappeared and then returned (page 339, 3rd full paragraph).

Accordingly, the cited art does not prove efficacy in treatment of withdrawal symptoms. The Examiner's position is that it would have been obvious to optimize the time intervals and divide portions of known daily effective doses of 2 mg/day, although these doses were not effective and the results were variable as discussed in this paragraph. However, the Examiner fails to describe where that motivation comes from, other than stating that "[o]ne would have been motivated to optimize the dosing intervals and optimize the daily amounts in portions to achieve an ultimate therapeutic regimen needed for individual patient's medical requirements." This assertion does not describe why one would be motivated to change Gerra, which divides a 2 mg/day dosage of flumazenil over two 24-hour periods, or Nutt, which administers a single dose of 2 mg in one minute (both are silent regarding a reduction in the desire to drink) or Soderpalm who showed no effect of flumazenil. Simply put, the references, alone or in combination, do not teach or suggest any benefit to changing their dosing regimens in order to arrive at sequentially administering flumazenil in doses of between about 0.1 and 0.3 mg of flumazenil at time intervals between about 1 and 15 minutes. The Examiner has not stated any scientific or medical rationale why a skilled artisan would seek to modify these ranges, specifically considering that the Gerra and Nutt references are directed toward evaluating the efficacy of flumazenil on withdrawal symptoms (a different objective), not decreasing the cravings and desire to drink alcohol. A skilled artisan would not modify Soderpalm's dosage or even consider combining Soderpalm with Gerra and Nutt to derive Applicant's claimed regimen as Soderpalm, who administers a very large dose (more than 350 times Applicant's dose) demonstrates no effect of flumazenil alone on alcohol taste reactivity in rats. There is simply no teaching, suggestion or

motivation in the cited references, alone or in combination, that would lead one to extensively experiment with sequential low doses of flumazenil to arrive at different administration dosages and timing intervals to treat a different condition and reduce the desire to drink alcohol.

In view of the preceding arguments, the claimed methods of reducing the desire to drink alcohol, are not obvious in view of Gerra and Nutt in combination with Soderpalm. These references – whether take alone or in combination – fail to teach, suggest or provide motivation to derive Applicant's claimed method. In fact, absent the teachings of the present specification, one of ordinary skill would fail to arrive at the claimed methods, and as the Examiner knows, using that kind of hindsight is impermissible. For at least these reasons, Applicant asserts that the rejection in view of Gerra, Nutt and Soderpalm under 35 U.S.C. §103(a) has been overcome and requests its withdrawal.

E. Claims 56 and 57 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gerra in view of Nutt as applied to claims 17-26 and 29 in view of Soderpalm as applied to claims 30, 46-55, 58-68 and 71 above and further in view of Opitz (clomethiazole (claim 56), piracetam and disulfiram (claim 57)). Claims 56 and 57 are canceled, rendering moot their rejection.

F. Claims 69 and 70 are rejected under 35 U.S.C. §103(a) as unpatentable over Gerra in view of Nutt as applied to claims 17-26 and 29 in view of Soderpalm as applied to claims 30, 46-55, 58-68 and 71 above and further in view of Opitz (clomethiazole (claim 69), piracetam and disulfiram (claim 70)). Claim 69 is canceled, rendering moot its rejection. Claim 70 is amended to delete the words piracetam and disulfiram, rendering moot its rejection.

Conclusion

For at least the above reasons, Applicant respectfully asserts that the claim rejections under 35 U.S.C. §103 have been overcome. Applicant respectfully requests allowance of the pending claims and issuance of a patent in due course. If there remain any additional issues to be addressed, the Examiner is invited to contact the undersigned at 404.745.2470.

Respectfully submitted,

/John K. McDonald/
John K. McDonald, Ph.D.
Reg. No. 42,860

KILPATRICK STOCKTON LLP
1100 Peachtree Street
Suite 2800
Atlanta, Georgia 30309-4530
Tel. (404) 745-2470
Fax. (404) 541-3297
General Fax. (404) 815-6555
Attorney Docket No: 55979-0100US (314589)